CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S-005

MEDICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Drug Evaluation and Research
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)

Lodine XL
(etodolac extended release tablets)

NDA 20-[ ]

Medical Officer Review

Submission date:	October 12, 1999
Received date:	October 12, 1999
Review date:	December 12, 1999
Drug Name:	Lodine™XL tablets
Generic name:	etodolac extended release tablets
Applicant:	Wyeth-Ayerst Research Division of American Home Products P.O. Box 8299 Philadelphia, PA 19101-8299
Pharmacologic category:	Nonsteroidal anti-inflammatory
Proposed Indication:	Juvenile rheumatoid arthritis
Dosage Form and Route:	Oral tablet
Submission type:	Pediatric exclusivity (SE5-005)

/S/

(James Witter, M.D., Ph.D. Medical Officer)

Orig NDA # 20-584
HFD-550/Div File
HFD-550/PM/Cook
HFD-550/Chem
HFD-550/Biopharm/Bashaw
HFD-550/MO/Witter
HFD-550/TL/Goldkind
HFD-550/DS/Midthun CM 8-8-00

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Background and Overview:

Lodine XL (Lox), which is an extended-release formulation of Lodine (T_{max} for Lodine= 1.4 h; for Lodine XL= 6.7h), is indicated for the management of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. A labeling supplement (NDA 20-584/S-003, submitted November 11, 1999) allows for the use of 1200 mg of Lox daily depending on the patient's response. Lodine, the trademark for etodolac, belongs to the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAID). Etodolac is the USAN name for the chemical compound (±)1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers.

On July 15, 1998, Wyeth-Ayerst submitted a letter to the Division of Anti-inflammatory, analgesic and ophthalmic drug products (HFD-550) requesting a "Written Request" for the conduct of a clinical trial of Lox in pediatric patients with juvenile rheumatoid arthritis (JRA). This letter was sent by HFD-550 on February 3, 1999 (Appendix A). In compliance with the provisions of Section 505A of the Federal Food, Drug and Cosmetic Act (Section 111 of the FDA Modernization Act of 1997), Wyeth-Ayerst has requested that 6 months of market exclusivity be granted for Lox. Based upon the "Written Request" letter, the following two studies were submitted:

> **"A 12-week, open-label study of etodolac administration in patients with juvenile rheumatoid arthritis, including an optional 8-week extension."**
> **(Clinical study report-CSR 37670 of protocol 0654D1-386-US)**

The pharmacokinetic (PK) parameters for the JRA patients treated in this open-label trial were compared with the PK results from adult RA patients as follows:

> **"Population pharmacokinetic analyses of etodolac in patients with active rheumatoid arthritis and in patients following oral surgery."**
> **(General Medical Report-37835)**

It has previously been noted in patients with JRA given immediate-release etodolac that the PK profile was similar to that in healthy adults receiving a single 400 to 500 mg dose of etodolac. This PK study was conducted to ensure that Lox may be administered in therapeutically relevant doses to obtain appropriate labeling information as well as additional safety data.

> *Reviewer's comment:* This review will primarily focus on the JRA open-label study. Those interested in the PK characteristics of Lox should read the PK review. Both the open-label and PK studies comprised 5 volumes. Areas in this review that specifically address a criterion in the "Written Request" letter will be highlighted *as follows*.

Clinical Protocol (0654D1-386-US) Synopsis:

Objectives:
The primary objective of this protocol was to examine the safety profile in pediatric patients with JRA after treatment with Lox for the initial 12-week open-label portion. The secondary objective was to evaluate the efficacy and PK of Lox in these same patients as well as characterize the safety and efficacy of Lox in JRA patients who participated in the 8-week open-label extension.

Study design/duration/date/ethical conduct:
As noted above, the study had two outpatient segments, segment I (an initial *12-week* open-label treatment period) and segment II (an optional, up to *8-week extension* of the open-label treatment, for those patients who had completed segment I). Patients discontinued all NSAIDs/ASA for a washout (or **flare) period** equal to 5 half-lives and not less than two days for screening. Acetaminophen (APAP) at age appropriate doses was allowed between screening and baseline for relief of arthritic symptoms but APAP was not allowed for 24 hours before any scheduled study visit. All patients completed a 2-week poststudy follow-up visit. This study was conducted between February and September, 1999.

Written informed consent was obtained from each patient and his/her parent or guardian before participation in either segment of this study.

Financial Disclosure
In accordance with 21 CFR part 54, a signed form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was included. Thirty-two (32) of 35 the clinical investigators for Study 386-US were listed under section 1 of Form 3454 [i.e. in compliance with 21 CFR 54.2(a)(b)(f)]. The remaining three clinical investigators did not supply forwarding addresses since the site was no longer available.

Protocol amendments:
On April 24, 1999, an amendment added extra study sites and defined the segment II extension.

Number of Patients/Demographics:
Seventy-two (72) patients (81 screened) were enrolled into segment I of this study from 11 centers (14 centers noted in summaries but 3 centers, Drs. Cawkwell, Stein and White, did not enroll any patients). As can be seen in Table 1, *of these 72 patients, 31 were < 12 years while 41 were ≥ 12 years. Most patients (68%) were female, white (68%), and had no history of asthma (86%). Most patients less than 12 years of age had pauciarticular JRA (55%) and most 12 years or older had polyarticular JRA (56%).*

Table 1: Demographic and Baseline Characteristics of Patients by Age Group

Characteristic	Age < 12 yr. (n=31)	Age ≥ 12 yr. (n=41)	Total N=72
Age (mean ± SD)	8.6± 1.5	13.8± 1.4	11.5± 2.9
Sex, n (%)			
Female	22 (71)	27 (66)	49 (68)
Male	9 (29)	14 (34)	23 (32)
Race, n (%)			
Black/Hispanic/Asian/Other	9 (29)	14 (34)	23 (31)
White	22 (71)	27 (66)	49 (68)
JRA diagnosis, n (%)			
Pauciarticular	17 (55)	15 (37)	32 (44)
Polyarticular	11 (35)	23 (56)	34 (47)
Systemic	3 (10)	3 (7)	6 (8)
Asthma history			
No	28 (90)	34 (83)	62 (86)
Yes	3 (10)	7 (17)	10 (14)

Disposition of patients

There were 59 patients that completed segment I while 13 patients withdrew. There were then 13 patients that subsequently enrolled in segment II while 46 did not continue either because the investigator or patients chose not to continue the patient into segment II or because the sponsor had closed the study. Of these 13 patients who entered segment II, 6 patients completed while 1 patient withdrew and the remaining 6 patients were not to complete the study since it was closed by the sponsor. Overall, 70 patients were analyzed for efficacy, 72 for safety, and 59 for PK.

Treatment administered/Prohibited therapy:

Lox was administered orally at a dosage based on body weight, 13.3-21.3 mg/kg , once daily as follows:

400 mg tablet x 1 (white label)	**20-30 kg**
600 mg tablet x 1 (yellow label)	**31-45 kg**
400 mg tablet x 2	**46-60 kg**
500 mg tablet x 2 (green label)	**>60 kg**

There were 41 patients that received Lox for more than 84 days.

As mentioned above, APAP could be used as a rescue medication as needed. Oral corticosteroids were permitted at doses up to 10 mg/d (or to 0.2 mg/kg/d). DMARDs (sulfasalazine, methotrexate, gold, hydroxychloroquine, [redacted] were permitted as per the inclusion criteria below.

Prohibited medications included ASA and other NSAIDs (including those OTC), tramadol, investigational drugs, anticoagulants, and antitubercular therapy or prophylaxis.

Inclusion criteria:

Patients were enrolled in *segment I* of the study if they satisfied the following criteria:

1. **Male and nonpregnant female, age 6-16 years, who had definite JRA by the ARA (1977) criteria who needed NSAID therapy. Patients must have been on stable DMARDs for 3 months, all other medications four weeks.**
2. **For girls of Tanner stage II or greater, a negative urine pregnancy test at screening, baseline and study visits.**
3. **Normal physical exam and laboratory results with the exception of those directly related to JRA.**
4. **A high probability for compliance and completion of the study.**
5. **Written consent provided by both patient and parent/guardian.**

Patients were enrolled into *segment II* of the study if they satisfied the above criteria along with the following:

1. **Patient tolerated and benefited from Lox treatment without clinically significant AEs.**
2. **Patient completed the entire segment I.**

Exclusion criteria:

Patients were excluded from participation in *segment I* of the study if they fulfilled any one of the following criteria:

1. **Have not tolerated etodolac or with a history of NSAID (including OTC) hypersensitivity**
2. **History or presence of significant allergic conditions**
3. **Significant medical or psychiatric disorder other than those related to JRA**
4. **History of GI bleed/ulcer**
5. **Major surgery within 6 weeks or any surgery planned during the study.**
6. **Current malignancy, recent or current severe infections, or conditions likely to interfere with drug PK.**
7. **History or presence of drug and/or alcohol abuse.**
8. **Condition requiring new drug therapy during this study.**
9. **Use of other investigational agents within 3 months of study including intra-articular (IA0 steroids within 1 month.**
10. **Any acute illness within 1 week before study baseline.**
11. **Inability to swallow solid oral dosage forms.**

Patients were excluded from participation in *segment II* of the study if they fulfilled any one of the above criteria in addition to the following:

1. **The emergence or exacerbation of any clinically significant AE or laboratory abnormality during segment I.**

2. **Early withdrawal during segment I.**

Removal of Patients from Therapy or Assessment:
Treatment could be discontinued and patients could be removed from the study for any of the following reasons:

1. **Adverse reaction**
2. **Other medical event**
3. **Failure to return**
4. **Unsatisfactory response (lack of efficacy)**
5. **Protocol violation**
6. **Other nonmedical event**
7. **Patient request (unrelated to study)**
8. **Remission of JRA**

Table 2 summarizes the discontinuations for patients in either segment I or II of this study. Reasons for these withdrawals and other information on these patients can be found in Table 7.

Table 2: Discontinuations from Segment I or II[a]

Reason for withdrawal	Age < 12 yr. (n=31)	Age ≥ 12 yr. (n=41)	Total N=72
Any reason	9	11	20
Adverse reaction	0	2	2
Failed to return	1	2	3
Pt/subject request	1	0	1
Lack of efficacy	3	2	5
Protocol violation	0	1	1
Study closed	3	3	6
JRA remission	1	1	2

a: 13 of 20 patients withdrew during segment I

Statistical methods:
For the primary and secondary efficacy variables, the median change from baseline was compared to zero by using the sign test. The paired t-test was used to test whether the mean change from zero was significantly different. The effects of demographic factors such as age, weight, sex, race, and baseline severity on efficacy variables were

evaluated through a series of univariate chi-square or Fisher's exact tests on the basis of the JRA DOI. All tests of significance were at the level of $\alpha=0.05$ (two-sided). Data from all patients who received at least 1 dose of study drug and provided at least 1 post-baseline assessment were included in the ITT efficacy analysis for segment I. Both a timepoint (observed cases) and a LOCF endpoint analysis were performed at weeks 2,4,8 and 12 for each variable. For the optional segment II, only a time-point analysis of the data from patients who participated was performed. Incidence rates of AEs and premature withdrawals were calculated.

Efficacy Assessment:

Each patient was examined by the same physician throughout the trial. Patients were evaluated at the screening, baseline, and all study timepoints (week 2, 4, 8, 12 and 20) in section I, II and 2-week post study period. For all timepoints there was an allowed window (i.e. week 4 ranged from 22-42 days) for the visit. The following efficacy variables were assessed at each visit (* indicates primary efficacy variable; + indicates variable in JRA Core Set-see below) *to address clinical responses*:

1. **Investigator overall assessment (*+)**
   (10 cm VAS from 0= asymptomatic to 10=severe symptoms)
2. **Patient overall evaluation (*+)**
   (Children were asked "How severe have your arthritis symptoms been within the past week?" Responses were on a 10 cm VAS from 0= asymptomatic to 10=severe symptoms)
3. **Parent overall evaluation (*+)**
   (same basic question/rating as for patient)
4. **Number of joints with active arthritis (*+)**
   (Based on 69 joints. Swelling graded 0 to 3 with 0=no swelling and 3 = severe swelling. A joint was considered active if it was swollen or if limited motion was accompanied by pain and tenderness. The hips and spine were considered active if the pain and tenderness existed i.e. hips and cervical spine were excluded from a grading of swelling)
5. **Number of joints with limited range of (LOM) motion (*+)**
   (Based on 69 joints. LOM was graded on a scale of 0 to 4 with 0=full range of motion, 1=1-25% LOM, 2=26-50% LOM, 3= 51-75% LOM and 4=76-100% LOM.)
6. **Morning stiffness**
7. **ESR (+)**
8. **Childhood Health Assessment Questionnaire (CHAQ), segment I only (+)**
   (A composite score based on 52 questions)
9. **Amount of pain in last week**
10. **Number of swollen joints**
11. **Number of tender joints**
12. **Number of joints with pain on motion**

To explore whether demographic factors such as age, weight, sex, race, and baseline severity affected clinical response, a series of univariate chi-square or Fischer's exact tests were performed where the demographic variables served as the independent variable and the **JRA definition of improvement (DOI)** served as the response variable. This DOI is based on the JRA Core Set Criteria identified above as (+). **The JRA DOI analysis was performed with the data from week 4 only**, any patient who withdrew before week 4 was considered a non-responder. To be designated as a responder, the patient had to have a ≥ 30% improvement in at least 3 of 6 criteria and while not experiencing a ≥ 30% worsening in more than 1 of these 6 assessments. The patient and parent global are considered as one variable. To determine a response, the patient's global was considered first for this assessment. If the patient did not provide an answer, the parent's global assessment was used.

Pharmacokinetic samples (*consisting of one 3-mL blood sample*) were collected at baseline and during the week 2, 4, 8 and 12 (or final) study visits for analysis of etodolac concentrations [redacted] It was noted that since patients did not always attend visits as scheduled, blood samples were also not always obtained as scheduled. Plasma samples for PK analysis were obtained from only 4 patients at week 12.

Efficacy results:

Reviewer's comment: Since there were so few patients entered into segment II, and since this portion of the trial was terminated early, no efficacy results will be presented from this section of the trial.

The results for the primary efficacy variables, as selected by the sponsor, are presented below in Table 3 for the various time points and endpoint of the trial. Compared to baseline, the physician global score and number of joints with LOM seemed responsive to improvement throughout the trial whereas the parent/patient global score and the number of active joints suggested improvement at differing points in the trial. Overall, there was considerable variability in all the parameters at the various assessment points.

Table 3: Primary Efficacy Variables-Endpoint (LOCF) Analysis-Segment I only

Variable (mean values noted)	Segment I (week) 2 n=64	4 n=68/69	8 n=69/70	12 n=69/70
MD overall score				
Baseline	3.8	3.6	3.7	3.7
Score	2.7	2.3	2.2	2.4
Change from baseline	1.0±2.2*	1.3±2.0*	1.4±2.4*	1.2±2.4*
% change from baseline	25.9±49.7	32.9±53.6	30.8±72.9	31.3±58.4
Patient overall score				
Baseline	3.7	3.6	3.6	3.6
Score	3.1	2.7	2.6	3.1
Change from baseline	0.6±2.3	0.8±2.3*	0.9±2.8*	04.±2.8
% change from baseline	14.8±49.8	9.0±85.0	8.4±121.5	-2.3±109.1
Parent overall score				
Baseline	3.6	3.5	3.5	3.5
Score	3	2.6	2.7	2.9
Change from baseline	0.6±2.2*	0.8±2.2*	0.7±2.2*	0.6±2.5
% change from baseline	12.3±46.6	15.8±58.7	9.8±97.5	11.3±69.2
Number of Active Joints				
Baseline	6.2	5.9	5.9	5.9
Score	4.9	4.1	3.7	4.3
Change from baseline	1.1±6.4	1.7±5.5*	2.0±6.4*	1.5±5.3*
% change from baseline	3.3±91.3	16.1±66.4	1.2±117.2	6.4±111.6
Number of joints with LOM				
Baseline	4.2	4.0	4.0	4.0
Score	3	2.7	2.6	2.7
Change from baseline	1.3±4.3*	1.4±4.2*	1.5±4.4*	1.3±4.6*
% change from baseline	15.1±58.4	28.0±64.1	22.1±83.9	18.5±95.3

* Significant at <0.05 level.

The results for the secondary efficacy variables, as selected by the sponsor, are presented below in Table 4 for the various time points and endpoint of the trial. Compared to baseline, the CHAQ, pain in last week, number of swollen joints and number of joints with pain on motion seemed responsive to improvement throughout the trial whereas the number of tender joints suggested improvement only near the end of the trial. There was no apparent significant change from baseline in the duration of morning stiffness and the ESR. Once again, overall, there was considerable variability in all the parameters at the various assessment points.

Table 4: Secondary Efficacy Variables--Endpoint (LOCF) Analysis-Segment I

Variable (mean values noted)	Segment I (week)			
	2 n=64/65	4 n=67/69	8 n=68/70	12 n=68/70
Duration of Morning Stiffness (min)				
Baseline	78	75	73	73
Duration	104	57	34	74
Change from baseline	-26±357	18±256	40±300	-.3±301
% change from baseline	-845±4856	-7±268	18±252	-41.1±356
ESR, mm/h				
Baseline	17	17	17	17
Score	17	18	16	16
CHAQ score				
Baseline	0.5	0.5	0.5	0.5
Score	0.4	0.3	0.4	0.3
Change from baseline	0.1±0.3*	0.2±0.4*	0.1±0.4*	0.2±0.4*
% change from baseline	29.7±48.0	29.8±121.7	23.8±117.1	47.7±57.3
Pain in Last Week				
Baseline	3.5	3.4	3.4	3.4
Score	2.8	2.4	2.6	2.8
Change from baseline	0.6±2.6*	1.0±2.5*	0.8±2.6*	0.6±2.5*
% change from baseline	16.5±61	18.0±93.6	-3.9±148.3	21.3±62.4
Number of Swollen Joints				
Baseline	5.3	5.1	5	5
Score	4.6	3.7	3.4	3.8
Change from baseline	0.5*5.2	1.2±4.9*	1.4±5.3*	1.0±4.1*
% change from baseline	8.1±78.4	16.5±74.9	1.8±108.6	13.4±83.7
Number of Tender Joints				
Baseline	2.4	2.2	2.2	2.2
Score	1.7	1.3	0.8	0.9
Change from baseline	0.7±6.2	0.9±5	1.4±5.2*	1.2±4.5*
% change from baseline	-27.5±275	7.3±190	21.5±127	22.1±117
Number of Joints with Pain on Motion				
Baseline	3	2.8	2.8	2.8
Score	1.3	1.1	1	1
Change from baseline	1.7±4.8*	1.7±4.5*	1.8±4.8*	1.8±4.6*
% change from baseline	24.4±96.4	30.3±110.7	33.8±90	34.8±94.1

* Significant at <0.05 level.

Presented in Table 5 are the number and percentage of responders on the basis for the JRA DOI analysis. There were two patients (38605-0015 and 38612-0095) who had no post-baseline data and so were considered non-responders. Overall, 32 of the 72 patients (44%) were considered to be responders. However, these data would suggest that patients with polyarticular disease are more likely to respond to Lox, those with

systemic disease least likely to respond and patients with pauciarticular disease as having a response between these two extremes. The reasons for the differing responses is not obvious from the data in Table 5 since it would require knowledge of all the variables in all the patients to begin to properly interpret these data. However, in apparent agreement with the primary and secondary variables (Tables 3 and 4), it appears that the physician global, the parent/patient global, the LOM of joints, the number of active joints and the CHAQ were the most responsive to change overall. Similarly, the ESR appeared to be the least responsive of these variables.

Although not included here, an analysis (NDA Table 9.3.2.A) was conducted that evaluated the JRA DOI response based upon demographic or baseline variables (age, sex, weight, race, diagnosis, prescribed dose, baseline CHAQ, number of active joints, LOM, ESR). This analysis suggested that clinical response was consistent across different levels of these variables.

Table 5: JRA DOI Responder analysis

JRA subset (# pts)	JRA DOI responders	JRA core set response variable (%)*					
		CHAQ	ESR	MD global	Pt/parent global	LOM of joint	Active joints
pauciarticular (32)	12/32 (38)	7/12 (58)	4/12 (25)	12/12 (100)	8/12 (75)	6/12 (50)	7/12 (58)
polyarticular (34)	19/34 (56)	16/19 (84)	8/19 (42)	15/19 (79)	12/19 (63)	10/19 (53)	12/19 (63)
systemic (6)	1/6 (17)	-	1/1 (100)	1/1 (100)	1/1 (100)	-	-

* Response variables were as noted above in the efficacy assessment section.

Safety Review:

Safety assessments were based on reports of AEs and results of routine ***physical examinations and laboratory*** determinations. Complete physical exams and evaluation for AEs were conducted at screening and the completion of section I, II and the 2-week post-study period.

A treatment-emergent adverse event (TEAE) was defined as an AE that was not present when the active phase of the study began or, if the AE was present, it worsened during the study. The emergence of any TEAE was also sought by asking the question: "How have you been feeling since your last visit?" Both AEs and TEAEs were classified and tabulated according to a modified COSTART system. Adverse events were tabulated for the two age groups in this study (i.e. < 12 years, ≥ 12 years) and ***for patients with a history of asthma. Particular attention was given to GI events (PUBs), renal events (papillary necrosis, medullary changes), and hepatic events (enzyme elevations and severe hepatic reactions such as necrosis or liver failure).***

Owing again to the nature of this particular trial, the bulk of the exposure to Lox occurred during segment I of the study. Of the 72 patients originally enrolled in this trial, 72, 69, 66, 66, and 58 patients completed 1, 2, 4, 6 and 12 weeks respectively of Lox treatment (NDA Table 10.1.A). After completion of segment I, the numbers drop rapidly (i.e. 22 patients had 14 weeks of therapy) with only 1 patient having taken Lox for > 21 weeks. Therefore, the safety database does not included large numbers of patients exposed for long durations of time. However, every patient enrolled in this open-label study was included in the safety evaluation.

TEAEs, without regard to the investigator's opinion regarding causality from Lox, are presented in Table 6 according to body system and age group. In some instances, subheadings are included when considered pertinent. Overall, about 70% of the patients in either age group reported a TEAE. The most common AEs appear to be in the Digestive and Musculoskeletal systems. The percentage of TEAEs in the two age groups (< 12 years, > 12 years) suggests the occurrence of AEs is not related to age.

> ***Reviewer's note: The percentage of AEs noted in this trial for any particular system is, for the most part, consistent with (or lower than) the rate noted in the phase 4 evaluation of Lox 1200 mg in adults.***

Table 6: Summary of Treatment Emergent AEs (%) by Age Group[A]

Adverse event	<12 years (n=31)	>12 years (n=41)	Total (n=72)
Any AE (1 or more)	23 (74)	29 (71)	52 (72)
Body as Whole	12 (39)	10 (24)	22 (31)
infection	3 (10)	1 (2)	4 (6)
pain	3 (10)	2 (5)	5 (7)
Cardiovascular	0	2 (5)	2 (3)
Digestive[B, E]	11 (35)	15 (37)	26 (36)
abdominal pain	3 (10)	4 (10)	7 (10)
diarrhea	0	3 (7)	3 (4)
dyspepsia	3 (10)	2 (5)	5 (7)
nausea	2 (6)	5 (12)	7 (10)
vomiting	2 (6)	4 (10)	6 (8)
stools abnormal	1 (3)	0	1 (1)
Hemic/lymphatic	4 (13)	5 (12)	9 (13)
anemia/hypochromic	1 (3)	6 (15)	7 (10)
Metabolic/nutritional	1 (3)	0	1 (1)
Musculoskeletal	12 (39)	12 (29)	24 (33)
arthralgia	8 (26)	8 (20)	16 (22)
Nervous	4 (13)	9 (22)	13 (18)
headache	4 (13)	6 (15)	10 (14)
Respiratory[C]	7 (23)	11 (27)	18 (25)
pharyngitis	4 (13)	4 (10)	8 (11)
URI	2 (6)	5 (12)	7 (10)
Urogenital [D]	0	1 (2)	1 (1)
Skin and appendages	6 (19)	4 (10)	10 (14)
Special senses	2 (6)	2 (5)	4 (6)
Urogenital	0	1 (2)	1 (1)
Allergic reaction other than drug	0	1 (2)	1 (1)

A. Derived from Table 10.2.2.1A. Body systems are not necessarily the sum of the individual AEs since a patient could report more than one AE in the same body system.

B. There were no perforations, ulcers or episodes of bleeding noted in this trial. One patient (38605-0011) had guaiac positive stool with a decrease in Hgb and Hct with a negative barium swallow and UGI series; the patient did complete the study.

C. There was no obvious enrichment of AEs in the 10 patients with asthma enrolled in this study compared to patients without asthma. Two of these patients had symptoms but completed the study while one patient with asthma withdrew because of lack of efficacy. No anaphylactic reactions occurred in this study.

D. No patients were withdrawn for any renal AEs. In particular, there were not patients with the syndrome characterized by flank pain, hematuria and decreased renal function.

E. Two patients (38604-0008 and 38614-0122), both on methotrexate, had elevations of liver enzymes; both completed the study. Three patients (38602-0022 [2 mg/dl]; 38604-0082 [2.1 mg/dl]; 38614-0104 [1.8 mg/dl]) had elevations of total bilirubin not considered clinically significant.

Serious Adverse Events

There were 4 patients with SAEs. One patient (38606-0056) taking 1000 mg of Lox developed hallucinations and a syncopal episode and withdrew from the study; this patient had been noted to have hallucinations with other NSAIDs. Although the other three patients completed the study, they were evaluated for arthralgia and decreased Hct

and Hgb with a negative GI evaluation (38606-0016), decreased Hct and Hgb with a positive stool guaiac but negative UGI series and barium swallow (38605-0011), and one patient (38604-008) noted above who had elevations of liver enzymes with concurrent methotrexate therapy.

Withdrawals

The patients that were withdrawn from the study are listed in Table 7. Owing to the nature of this particular study, most patients withdrew from segment I. The patients withdrawn from segment II were done so (with one exception) due to termination of the study. There does not appear to be any pattern of withdrawal relating to the dose of Lox or the subtype of JRA.

Table 7: Patients withdrawn from Segment I or II*

Pt number	Pt description	Dose (mg) of Lox	Day withdrawn	Reason for withdrawal
segment I				
38601-0032	6 y/o, F, pauc	400	16	LOE/AE (arthralgia)
38601-0034	12 y/o, F, poly	600	15	protocol violation
38601-0070	14 y/o, M, pauci	600	53	AE (nausea)
38604-0006	16 y/o, F, pauci	800	43	lost to follow-up
38604-0085	13 y/o, M, poly	1000	70	LOE
38605-0015	12 y/o, M, systemic	800	4	LOE/AE (with pharyngitis)
38606-0056	14 y/o, F, poly	1000	79	AE (hallucinations,syncope)
38611-0058	15 y/o, F, poly	1000	43	lost to follow-up
38611-0059	11 y/o, F, poly	600	4	Pt request
38611-0061	13 y/o, M, poly	600	78	remission
38611-0108	7 y/o, F, systemic	400	41	remission
38612-0095	7 y/o, F, pauci	400	1	lost to follow-up
38614—106	7 y/o, M, pauci	400	15	LOE
segment II				
38601-031	10 y/o, M, poly	600	94	LOE/AE (synovitis)
38604-0010	12 y/o, M,-	600	-	administrative reasons
38601-0067	9 y/o, M, -	600	-	administrative reasons
38608-0071	7 y/o, M, -	400	-	administrative reasons
38608-0049	10 y/o, F, -	600	-	administrative reasons
38608-0050	14 y/o, M, -	600	-	administrative reasons
38601-0066	16 y/o, F, -	600	-	administrative reasons

* Pauci = pauciarticular disease; poly = polyarticular disease, LOE = loss of efficacy.

Deaths and hospitalizations

No patients died or where hospitalized during this study.

Pharmacokinetic results

As noted by the sponsor, patients with JRA were found to have a pharmacokinetic (PK) profile similar to that in healthy adults after receiving a single 400-to 500- mg dose of immediate-release etodolac. The PK portion of this study was conducted to examine the PK profile of Lox in patients with JRA to ensure that it was administered in therapeutically relevant doses. As noted in this study, patients given Lox in doses of 400 to 1000 mg (13.3-21.3 mg/kg body weight) once daily exhibited PK disposition of Lox similar to that seen in healthy adults.

> ***Reviewer's comment: Details of the pharmacokinetics aspects of this study can be found in the PK review.***

Bioanalytical results were based on 139 observations of etodolac concentrations available from 59 patients. The mean (95% CI) CL/F was 0.048 (0.043 to 0.053) L/h/kg which is in range of the mean clearance (0.053 L/h/kg) from a previous single-dose study of etodolac immediate-release in patients with JRA. However, the mean (95% CI) V/F of 0.789 L/kg appeared higher than the mean previously observed (0.488 L/kg). Compared to adult RA patients, it appears that the CL/F and volume of distribution were lower while the $t_{1/2}$ was longer in patients with JRA.

It is expected that once daily dosing with Lox in JRA would yield concentrations approximately 27% higher than values following a single dose. The lack of a significant covariate relationship with CL/F or V/F suggests that adjustment of doses based on body weight adjustment may not be necessary for patients with JRA.

Conclusions/Discussion:

Efficacy

Owing to the nature of this single trial (open-label, no controlling arm), no adequate comparative assessment of Lox is possible from the data submitted. The data obtained suggests that Lox (at doses ranging from 13.3 mg-21.3 mg/kg) did result in improvements in the physician, patient and parent overall scores along with the number of active joints, number of joints with LOM and CHAQ throughout most of the duration of the trial as compared to baseline during segment I of this trial.

However, it is of interest to examine the responses with regards to the JRA DOI (Table 5) across the subsets of JRA as noted at the 4-week endpoint. It would appear that there was a more robust response in patients with polyarticular as compared to pauciarticular disease. This difference, at least in responders, does not seem to reflect differences in response to treatment as assessed at the level of the joint (i.e. number of active joints or LOM). However, without all the outcomes for these JRA DOI core variables from all patients, it is difficult to make meaningful inferences. Nonetheless, the differing responses do not seem to reflect preferential discontinuations due to lack of efficacy in the pauciarticular population (Table 2). Therefore, it would seem to be a reasonable

conclusion from these data that the JRA DOI could be utilized as a primary efficacy variable in trials that enroll JRA patients with both polyarticular and pauciarticular disease. There are not enough patients with systemic disease to make any useful comparisons.

Safety

As noted by the sponsor, the primary objective of this trial was to evaluate the safety of Lox according to the dosing schedule as utilized. Once again, especially without some arm for comparison, it is difficult to understand how any of this information can be placed into a proper context short of historical controls either in an adult or pediatric population.

Nonetheless, no patients died or were hospitalized during the study. There were no withdrawals for serious GI, renal, or hepatic events or because of abnormal clinical laboratory events. Patients with a history of asthma did not seem to experience an excess of AEs compared to those patients without asthma. There were 4 patients noted to have potentially clinically important adverse events which included a patient with hepatitis (possibly due to methotrexate), a patient with a positive stool guaiac, a patient with anemia (both with a negative GI workup) and one patient with syncope and hallucinations; of these, three patients completed the study. Five patients withdrew due to adverse events noted as pharyngitis, nausea, syncope and hallucinations, synovitis and arthralgia.

Overall, Lox (at doses not exceeding 20 mg/kg) appeared to be tolerated in this patient population. The pattern and frequency of AEs do not seem to be substantially different than those noted in the adult arthritic population given Lox at doses up to 1200 mg/d.

Label review:

Proposed changes (indicated by **bolding and underlining**) by the sponsor to the label involved the Pediatric portion of the **Special Populations** section, the **Clinical Trials** section and **Pediatric Use** section; only the latter two will be commented on here. The Pediatric portion of the Special Populations will be addressed in the PK review.

Clinical Trials

Arthritis

In the first paragraph, the word **adult** was added between 1552 and patients.

A new second paragraph as follows was proposed:

The safety, efficacy, and pharmacokinetics of Lodine XL were assessed in an open-label, 12-week clinical trial. Seventy-two (72) patients, aged 6-16 years old, with juvenile rheumatoid arthritis, received Lodine XL in doses of 400 to 1000 mg (13.3-21.3 mg/kg body weight) once daily. At these doses, Lodine XL controlled

the signs and symptoms of juvenile rheumatoid arthritis. Based on the results of this study, the safety profile of Lodine XL (at doses not exceeding 20 mg/kg) appeared to be similar to that observed in the adult arthritic patients in clinical trials.

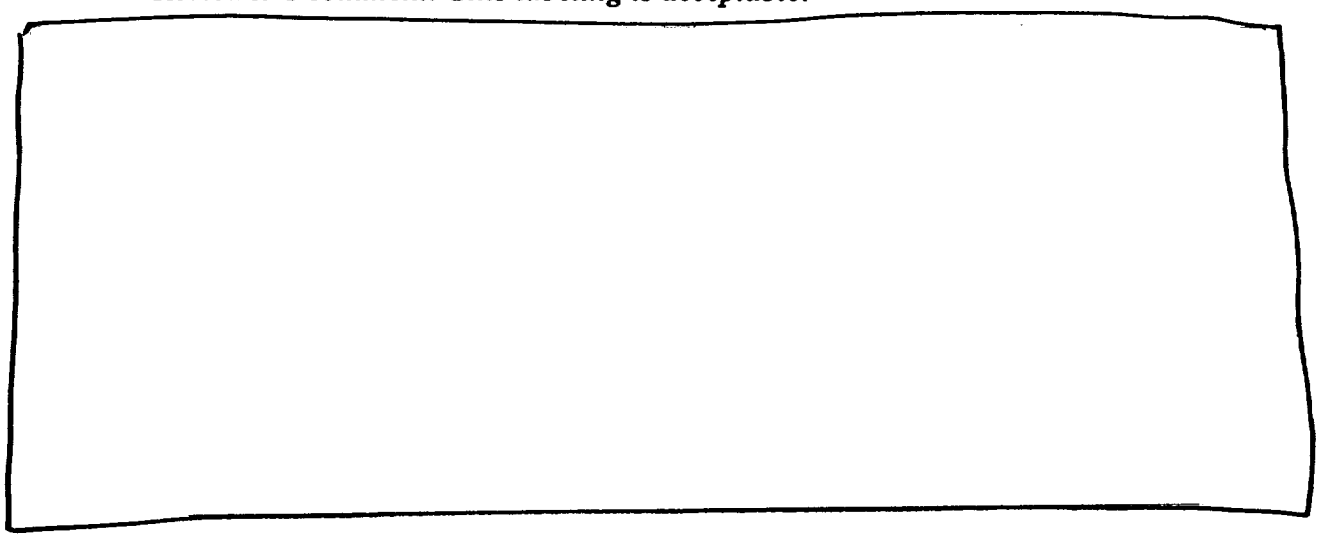
Reviewer's comment: This labeling is acceptable.

Pediatric Use

The original sentence (Safety and effectiveness in pediatric patients have not been established) was removed and replaced with:

If a decision is made to use Lodine XL for patients six years of age or older, as with other NSAIDs, such patients should be monitored periodically. (See PRECAUTIONS_Laboratory Tests and CLINICAL TRIALS-Arthritis).

Reviewer's comment: This labeling is acceptable.



APPEARS THIS WAY
ON ORIGINAL